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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/139,425	08/25/98	ESMON C	OMRF-171

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1636	14

DATE MAILED: 02/14/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/139,425	Esmon et al.
Examiner	**Group Art Unit**
WILLIAM SANDALS	1636

☒ Responsive to communication(s) filed on *Dec 7, 2000*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-25* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) *1-4* is/are allowed.

☒ Claim(s) *5-7, 12, 13, and 15-20* is/are rejected.

☒ Claim(s) *8-11, 14, and 21-25* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Response to Arguments

1. Amendments to claim 1 in Paper No. 13, filed December 7, 2000 have overcome the rejection of claims 1-12 under 35 USC 112, second paragraph, and the rejections are withdrawn.

2. Arguments set forth in Paper No. 13 have overcome the rejection of claims 13, 15, 20 and 22 under 35 USC 102, and the rejection is withdrawn.

3. Arguments set forth in Paper No. 13 regarding the rejection of claims 5-6 and 16-18 under 35 USC 112, first paragraph have been considered but are not persuasive. The rejection is repeated below along with responses to the arguments. The rejection as it applied to claims 7 and 19 is withdrawn in view of the amendment to the claims.

4. New grounds of rejection are made hereinbelow.

Claim Objections

5. Claim 13 is objected to because of the following informalities: Claim 13 is indicated as being amended in Paper No. 13, but the claim has not been amended. Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 5-6, 12 and 16-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of selectively delivering genes to a large vessel endothelial cell nucleus by binding a conjugate to an endothelial protein C receptor (EPCR). While applicants have shown the binding of a conjugate to an endothelial protein C receptor (EPCR) *in vitro*, they have not demonstrated any *in vivo* delivering of a gene to an endothelial cell, which constitutes a method of gene therapy. In order to do so, undue experimentation is required. Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been summarized in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors as they apply to the instant claimed invention are as follows:

a- The quantity of experimentation necessary to reduce the instant claimed invention to practice would involve delivering a gene to an endothelial cell for gene therapy.

b- Only prophetic guidance and no examples of delivering a gene to an endothelial cell *in vivo* have been provided.

c- The nature of the invention is complex. Gene therapy is a new and developing art as recited in Marshall in the section titled "The trouble with vectors", and at page 1054, column 3, and at page 1055, column 3. The problems of gene delivery, gene targeting to reach the intended host cell, and then to reach the intracellular target are not yet solved, as taught in Verma et al. (see especially page 239, column 3, the box titled "What makes an ideal vector?" and page 242).

d- The prior art taught by Orkin et al. (see especially the section on "Gene transfer and expression" and "Gene therapy in man status of the field") described many problems in the developing field of gene therapy. Recited problems include: lack of efficacy, adverse short term effects and limited clinical experience, the inability to extrapolate experimental results and unreliability of animal models. Problems with the vector include: host immune response to the vector and the expressed product, difficulty of targeting the vector to the desired site, transient expression of the gene of interest and low efficiency of delivery of the vector to the targeted site.

e- The state of the art as taught by Verma et al., which states "the problems - such as the lack of efficient delivery systems, lack of sustained expression, and host immune reactions - remain formidable problems" and Anderson, W. F. (see page 25, top of column 1), which states "[e]xcept for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease".

f- Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

Response to Arguments

8. Applicants have argued in Paper No. 5, that the argument above pertains to viral vectors. In as much as the references discuss viral vectors, those sections which are specific to the use of viral vectors for delivery of a nucleic acid to a cell clearly do not apply to the instant claimed invention. However, the bulk of the content of the references discusses the application of gene therapy, which does apply.

The statement in Anderson, WF, makes it clear that the state of the art in gene therapy, or delivery of nucleic acids for therapeutic purposes, is still a poorly understood art, and the references provided by applicant, while encouraging, do not overcome the problems facing practitioners in the gene therapy art, and make it clear that applicants must provide detailed teachings on how to make and use such an invention. Since these teachings are not presented in the instant claims and specification, the instant claimed invention is not enabled.

9. Paper No. 10 asserts that the amendments to the claims avoid the rejection. This is not the case, since the rejection is centered on the use of nucleic acids in a therapeutic method, for "gene therapy". The claims and specification are not enabled for gene therapy, as set forth in the rejection above.

10. Paper No. 10 asserts that claims 7 and 19 have been rejected in error, since they are claiming "drugs and diagnostic agents". The term of the claims, "drugs" is not defined, and as such, embraces the use of nucleic acids as "drugs", which are not enabled (see above).

11. Paper No. 13 asserts that the claims have been amended to read on *in vitro*. This is not convincing since the provision for *in vitro* does not exclude the *in vivo* limitations of the claims.

12. Paper No. 13 asserts that literature articles produced in reference to the practice of gene delivery are enabling for the instant claims. Two of the references are after the instant filing date by a year, and are not permitted as evidence of enablement. The remaining reference teaches the ability to physically deliver nucleic acids to a cell *in vivo*. The physical delivery of a nucleic acid to a cell *in vivo* is not a limitation which applies to the rejection of the claims above and is therefore a moot point. Anderson, W.F. is contemporary with the instant filing date, and Anderson, W. F. makes it abundantly clear that the process of gene therapy is still an undeveloped and unpredictable art. The burden of proof of enablement on the teachings of the instant specification is high. Since the instant claimed invention has only one *in vivo* utility, namely, gene therapy, the referenced articles do not overcome the instant enablement rejection of gene therapy as set forth in the instant specification.

13. Claims 7 and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The amendment to the claims in Paper No. 13 has entered the language "non-nucleic acid drugs". The specification does not provide a description of this

term, and the term is not art defined. As such the term "non-nucleic acid drugs" constitutes new matter.

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 5, 7, 16 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

16. Claims 5 and 16 have been amended to recite "contacting the endothelial cells of large vessels with the nucleic acid molecule conjugate, either *in vitro*, by catheterization to the endothelial cells, or during a surgical procedure involving the endothelial cells to be contacted". The meaning of this amendment is not understood. How is a catheterization or surgical procedure performed *in vitro*? The language "either" seems to indicate that there is an option of performing the method *in vitro* or *in vivo*. There is also an inconsistency with the claim language and with the remarks section of Paper 13 at page 3 which states "the claims have been amended to recite that the EPCR is bound to the cells *in vitro*". Rewriting the claim to clearly indicate that the method is practiced *in vitro* would obviate the instant rejection.

17. Claims 7 and 19 have been amended to recite "non-nucleic acid drugs". No definition is provided in the instant claims and specification for the term. "Non-nucleic acid drugs" is not an

art defined term. Since the term merely excludes nucleic acids but does not provide the metes and bounds of the term "non-nucleic acid drugs", it is vague and indefinite.

18. ***Claim Rejections - 35 USC § 102***

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

20. Claims 13, 15, 19 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No. 5,254,532.

US Pat No. 5,254,532 taught (see column 2, lines 17-23, example 10 and claim 3) a simultaneous binding of activated protein C and protein S to an endothelial cell of a large vessel. Protein S is inherently bound to activated protein C on the endothelial protein C receptor on large vessel endothelial cells. The proteins therefore are "conjugated" when bound to the endothelial protein C receptor on large vessel endothelial cells. This inherency is shown in US Pat No. 5,852,171 at column 7, lines 43-55.

Allowable Subject Matter

21. Claims 1-4 are allowed.

22. Claims 8-11 and 21-25 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

23. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Richard Schwartz can be reached at (703) 308-1133.

Any inquiry of a general nature or relating to the status of this application should be directed to the Zeta Adams, whose telephone number is (703) 305-3291.

William Sandals, Ph.D.
Examiner
February 8, 2001

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER